AI for fun and serious puzzles

Bridging symbolic and numerical AI to learn how to solve Sudokus or design new proteins

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GdR IA - BIOSS seminar

Constraint network (X, C) — Feasibility biased

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- a solution is an assignment of X that satisfies all constraints (NP-complete)

Symbolic NP-complete AI: SAT, CSP, CP

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SAT and CP

- Algorithms to find a solution (Backtrack, unit/constraint propagation, clause learning...)
- CP: predefined constraints (AllDifferent,...)

A bit of bragging...

NP-complete: can express all NP-complete problems

- the logical puzzles you like (Sudoku, Nonograms...)
- or not (configuration, scheduling, test pattern generation...)
- robot planning
- digital circuit verification (Bounded Model Checking)
- or software verification (FOL, grounding, abstraction)
- recently proved the “Pythagorean triple” conjecture (200TB proof)[10]

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Standard argument for less realistic problem reformulation, heuristics or stochastic search

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NP-complete: can express all NP-complete problems

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- or not (configuration, scheduling, test pattern generation...) SIEMENS THALES
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- digital circuit verification (Bounded Model Checking) intel IBM
- or software verification (FOL, grounding, abstraction) cadence
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Real SAT instances with millions of variables/clauses can be solved (with a proof)

Is it bio-compatible?

Biology

- Many discrete object ($\{A, T/U, G, C\}$, amino acids, genes, alleles, enzymes...)
- Lots of experimental (noisy) data
- Biology has few “exact” rules

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Shift from boolean function to numerical cost functions

From boolean functions to cost functions

Cost function network (X, W) — Homogeneous feasibility and criteria

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Solvers: daoopt, toulbar2, MaxHS (MaxSAT)...

- Algorithms to find optimal solution (Branch and bound, cost function propagation)
- Predefined cost functions (Weighted All-Different,...)

Example: MAXCUT with hard edges

Graph $G = (V, E)$ with edge weight function w

- A boolean variable x_i per vertex $i \in V$
- A cost function per edge $e = (i, j) \in E$: $w_{ij} = w(i, j) \times \mathbb{1}[x_i \neq x_j]$
- Hard edges: constraints with costs 0 or $-\infty$ (when $x_i \neq x_j$)

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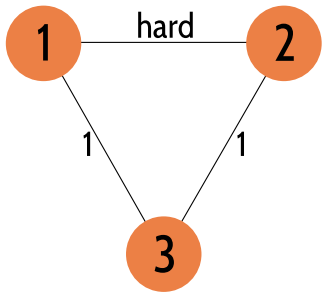
3-clique

- vertices $\{1, 2, 3\}$
- cut weight 1
- edge $(1, 2)$ hard.



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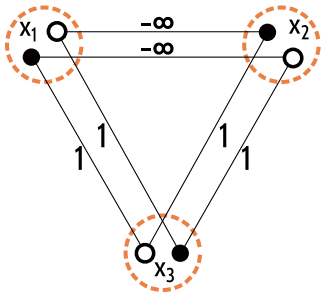

toulbar2 input file (Python API too)

MAXCUT on a 3-clique with hard edge

```
{
 "problem" :{"name": "MaxCut", "mustbe": ">0.0"},
 "variables": {"x1": ["l","r"], "x2": ["l","r"], "x3": ["l","r"]},
 "functions": {
     "cut12": {"scope": ["x1","x2"], "costs": [0,-100,-100,0]},
     "cut13": {"scope": ["x1","x3"], "costs": [0,1,1,0]},
     "cut23": {"scope": ["x2","x3"], "costs": [0,1,1,0]}
  }
}
```

Solving the Weighted Constraint Satisfaction Problem

Extensions of boolean reasoning to costs[21]

- Massive local reasoning provides (LP-related) lower bounds[5,6]
- Backtrack turned into (HBFS) Branch and Bound[1]
- Clever adaptive heuristics[3,12]
- On the fly variable elimination,[11] dominance,[2,6]...
- Graph-structure (treewidth/treedepth) aware[7]
- Guaranteed hybrid local search (VNS)[15]

Toulbar2 (github.com/toulbar2/toulbar2)

- Open Source C++ CFN solver (github.com/toulbar2/toulbar2)
- Won the UAI/Pascal “Approximate Probabilistic Inference Challenge” twice (and more)

Probabilistic Inference?

A CFN is a "Graphical Model"[8]

- Defines a joint non negative integer function on many variables
- Very close to Markov Random Field (Potts models): defines a probability distribution
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$$P(X) \propto e^{-W(X)}$$

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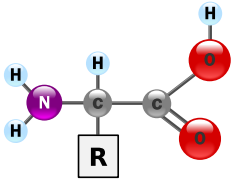
Toulbar2 solves MAP/MRF+constraints using automated reasoning algorithms Uncertainty Ok

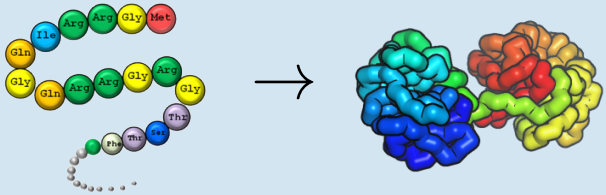
Proteins

Most active molecules of life

Sequence of “amino-acids”, each chosen among 20 natural ones



Folding

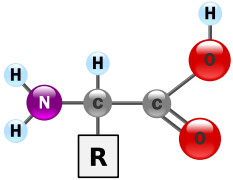


Transporter, binder, regulator, motor, catalyst...
Hemoglobine, TAL effector, ATPase, dehydrogenases...

Protein Design

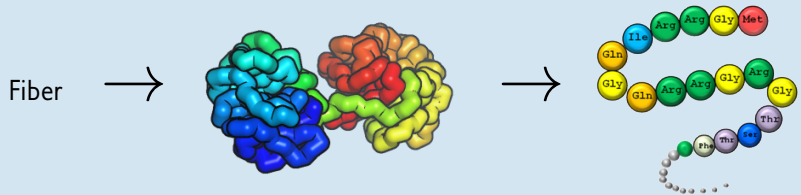
Most active molecules of life

Sequence of “amino-acids”, each chosen among 20 natural ones



Inverse folding

Fiber



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Why should we design new proteins

Eco-friendly chemical/structural nano-agents

- New components for nanotechnologies
- New catalysts (environment, biofuels, food and feed, cosmetics...),
- New drugs for medicine (antibodies,...)

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CPD: From bits to atoms — From information to functional matter

- mass 3d printing-like capacities at atomic level (bacterias, yeast, ...)
- structural and functional purposes (powerful origami)
- produced new folds,[9] catalysts,[19] nano-components[24]

Protein Design as the inverse of folding

Ingredients

- Full atom model of a protein backbone (assumed to be rigid)
- Full atom energy function (bonds, electrostatics, solvant, statistics...)
- Maximum stability $\equiv$ Minimum energy NP-hard[18]
- Catalog of all 20 amino acids in different conformations (≈ 400 overall)

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As a cost function network

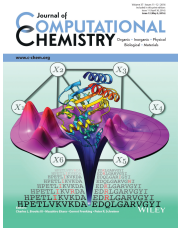
- One variable per position in the protein sequence
- Domain: catalog of amino acids conformations (rotamers)
- Function: decomposed pairwise energy
- Search space has size $\approx 400^n$

Exact vs. Stochastic search

Large input (> 1GB) — **NP-hard problem**

Toulbar2 is able to...

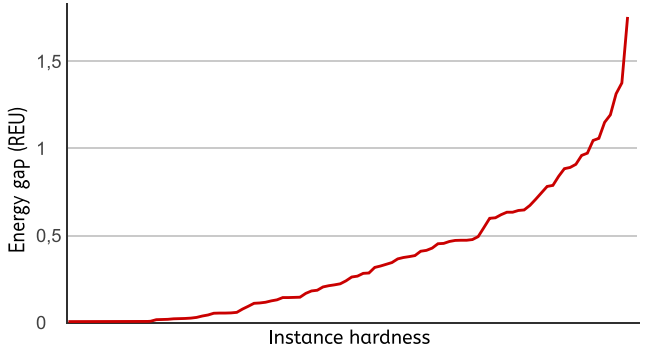
- provide a proven minimum energy solution
- exhaustively enumerate sequences close to it
- in spaces of size $> 10^{400}$



A highly tuned Monte Carlo Simulated Annealer increasingly fails to find the optimal sequence[a]

[a] David Simoncini et al. "Guaranteed Discrete Energy Optimization on Large Protein Design Problems". In: *Journal of Chemical Theory and Computation* 11.12 (2015), pp. 5980–5989. DOI: 10.1021/acs.jctc.5b00594.

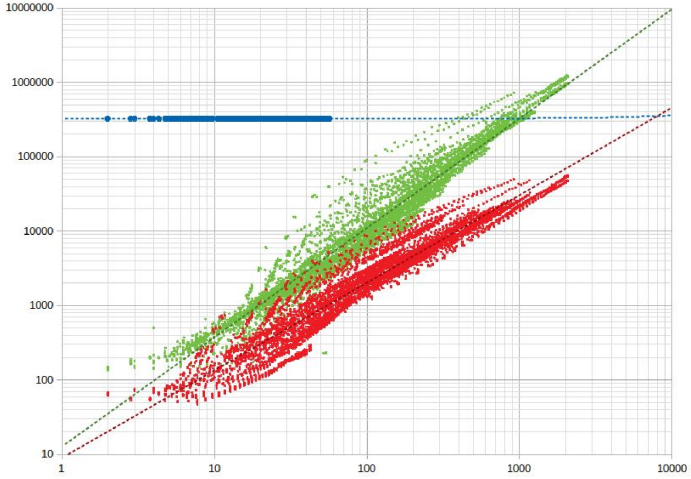
Unbounded error



Asymptote: **Size matters!**

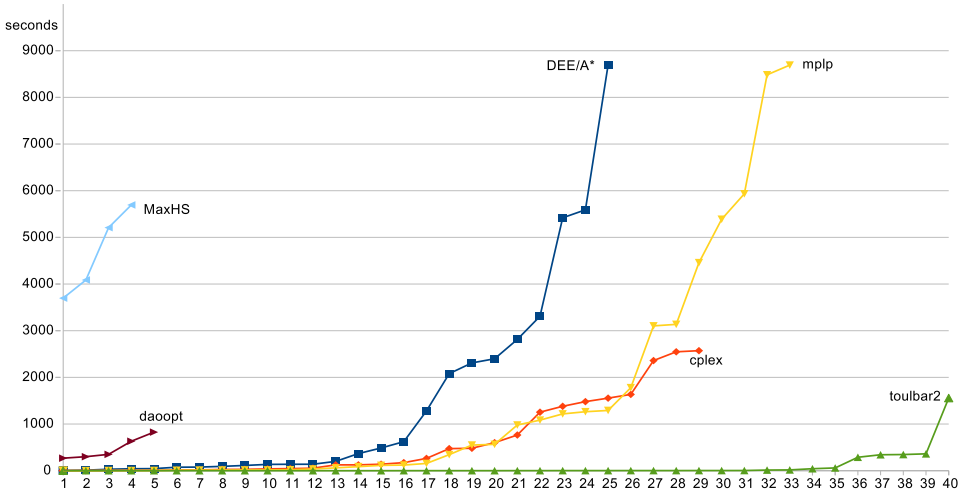
Asymptotic convergence can be arbitrarily slow...

Quantum computing (DWave),Toulbar2 & SA[13]



DWave approximations		*kcal/mol*
gap > 1.16, 90% of the time	> 4.35, 50% of the time	> 8.45, 10% of the time

Toulbar2 vs. CPLEX, MaxHS...(real instances)

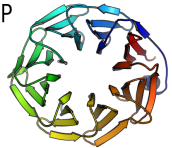


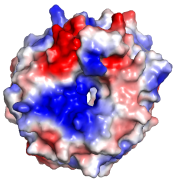
# of instances solved (*X*) within a per instance cpu-time limit (*Y*)

From bits to atoms (col. A. Vœt (KU Leuven), D. Simoncini[14])

C8 pseudo-symetric 2OVP symmetrized into a nano-component

2OVP





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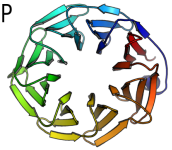
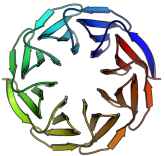
-  Tako: (R)evolution + Rosetta/talaris14 8 fold

2OVP



Tako



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-  Ika: toulbar2 + talaris14 — 4 fold

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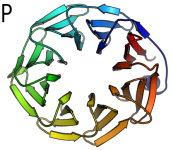

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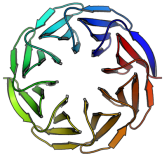

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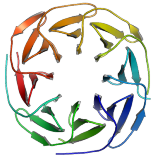

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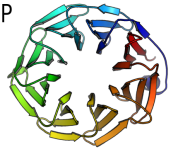

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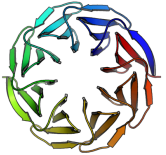

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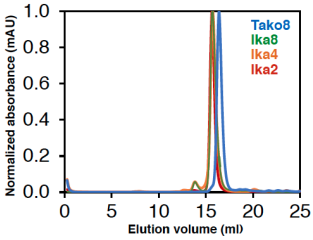
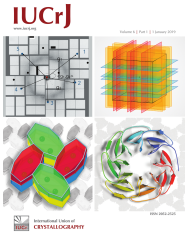
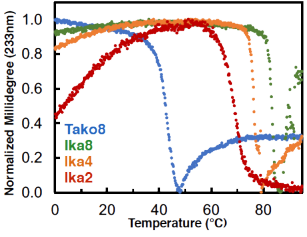
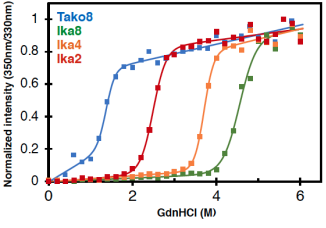




Assemble as 8-bladed propeller

- Ika* more stable than Tako8
- Temperature
- Chemical denaturation





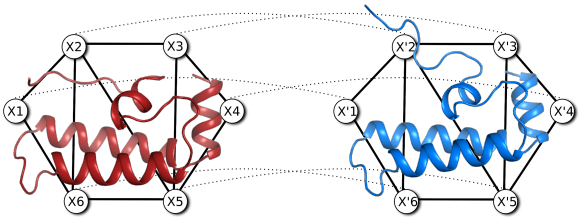
Multistate design accounts for protein flexibility

Optimize energy on several backbones

- Only desirable backbones (flexibility, switches,...): decision NP-complete
- Undesirable backbones (specificity, orthogonal design): Σ_2^p-complete

Positive multistate design[25]

Combine multiple CFN-models, connect them by sequence identity constraints



Positive multi-state design

Tested on 10 NMR and 10 X-Ray+backrub ensembles of 4 states

- large problems: more than 300 variables, several hundreds of values
- can be solved to optimality in reasonable time on one CPU corrected
- “slow” exponential growth of cpu-time as a function of input size

Native sequence recovery

- Fraction of amino acids of an existing proteins recovered by design
- Increases by an average of 16% (NMR) or 8% (X-ray+backrub) over single state design
- Better protein design with no algorithm design

Energy function

Imperfect

- Approximations: solvent effect...
- Ignored: polarisability, expressability...
- Needs more information, extracted from *data*

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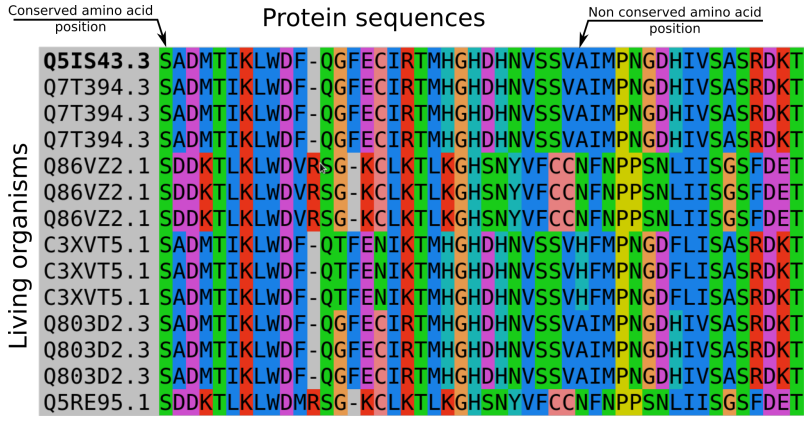
Evolutionary information

- Use similar proteins (homologs) from databases
- Multiple alignment: align similar regions of the sequences

A multiple alignment with conserved positions



Simple integration of information

- Force amino acid choice (constraint) at conserved positions.

Learning CFNs from data

Boltzman distribution connects probability and cost

$$P(X) \propto e^{-W(X)}$$

- Use (regularized) maximum-loglikelihood estimation
- Has a nice cost-domain interpretation

Learning in practice

Similar to contact-map prediction (CCMPred[22])

- We start from a complete pairwise CFN with unknown cost functions

Learning in practice

Similar to contact-map prediction (CCMPred[22])

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Efficient convex optimization based implementation

- Uses the Alternating Direction Multiplier Method[17]
- Approximate likelihood based (probabilistic input) + L1 (sparsity)
- Reasonably good performances, even in Python (numpy)

Designing a new nanobody scaffold

- Using Rosetta hybrid force-field and rotamer library
- Trying to satisfy several constraints (originality, resistance, composition...)
- Multi-state design[25]
- with MSA-extracted evolutionary preferences

In Protein design

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Limited experimental power

- Over 6 sequences designed without evolutionary information: 3 expressed
- Over 3 sequences designed with evolutionary information: 3 expressed
- Much more power in a recent Science paper[20]

But much more general (sparsity crucial)[4]

Can learn to play the Sudoku from examples

- Less examples, faster, better than RRN[16] or SAT-Net[26]
- With comparable or less biases
- and the ability to exploit perceptual "layers" output

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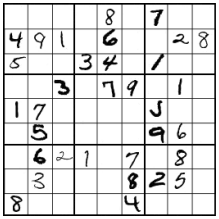

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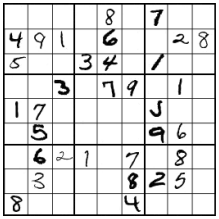

Learn user preferences for car configuration assistant — Renault/Hélène Fargier

- 8,252 historical configurations of an higly combinatorial van (2^{74} configurations)
- extra configuration constraints
- best results (accuracy) obtained when combining both ML and CP

Combines ML (data) and Automated reasoning (logic)

Let's recap...

- Model the problem as a CFN (generalizes CP): knowledge

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Let's recap...

- Model the problem as a CFN (generalizes CP): knowledge
- Learn other CFNs from available data sets (convex optimization,...)
- Combine the models by scaling/adding/connecting them together
- Add further design constraints/preferences: desired properties

Open source

https://github.com/toulbar2/toulbar2
https://github.com/toulbar2/CFN-learn

Combines ML (data) and Automated reasoning (logic)

Let's recap...

- Model the problem as a CFN (generalizes CP): knowledge
- Learn other CFNs from available data sets (convex optimization,...)
- Combine the models by scaling/adding/connecting them together
- Add further design constraints/preferences: desired properties
- Solve them with toulbar2 : −) to get your new design

Open source

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Thanks

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My apologies to those missing in these lists. Even imperfect lists seem better than simply no list

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